(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 July 2007 (26.07.2007)

PCT

(10) International Publication Number
WO 2007/083323 A2

(51) International Patent Classification:
A61K 38/08 (2006.01) *A61K 9/22* (2006.01)

(21) International Application Number:
PCT/IN2007/000022

(22) International Filing Date: 19 January 2007 (19.01.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
101/MUM/2006 23 January 2006 (23.01.2006) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** NOVEL ORAL DELIVERY OF DESMOPRESSIN AND ITS SALTS

(57) **Abstract:** The invention describes a modified release oral dosage form of desmopressin which upon administration releases two or more amounts of desmopressin. The dosage form comprises of individual dosage units, such as an immediate release dosage unit and one or more delayed release dosage units, each comprising of a suitable amount of desmopressin, released after a predetermined time interval. The dosage form of the invention provides a release profile, adapted such that the dosage form exhibits improved efficacy for a prolonged duration of action and provides for an overall superior management of antidiuretic therapy. The invention also provides for method of manufacture of the dosage form of the invention and also method of treatment of diseases such as diabetes insipidus, nocturnal enuresis, nocturia and urinary incontinence in a mammal in need of such treatment.

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NOVEL ORAL DELIVERY OF DESMOPRESSIN AND ITS SALTS

The present invention relates to oral dosage forms of desmopressin or a pharmaceutically acceptable salt thereof, to methods for their preparation and to their use in the treatment and prophylaxis of diseases in mammals, particularly humans.

BACKGROUND OF THE INVENTION

Desmopressin (l-desamino-8-D-arginine vasopressin, DDAVP), a nonapeptide, is an analogue of the hormone vasopressin. It is commercially available as the acetate salt in injection form, tablet form and as a nasal spray, and is commonly prescribed as an antidiuretic in the treatment of conditions like diabetes insipidus, nocturnal enuresis and urinary incontinence. Desmopressin injection is also indicated in maintaining hemostasis in certain types of Hemophilia A and Von Willebrand's disease (Type I). An oral tablet dosage form of Desmopressin is approved for the treatment of central diabetes insipidus and primary nocturnal enuresis.

The currently marketed desmopressin tablets are conventional immediate release dosage forms, which, at times, are needed to be given twice or three times daily to achieve the required level of antidiuresis. They often cause adverse effects related to water intoxication and hyponatremia, like headache, nausea/vomiting and bloating. This may possibly be due to prolonged water retention. Also, the dose of the tablets is quite high (0.1 – 0.2 mg) compared to the intranasal or intravenous doses, since oral bioavailability of desmopressin is only about 0.16%. (See, Physician's Drug Reference, page no. 2895, 60th Ed., Published by Thompson PDR, 2006)

Drugs like desmopressin, which have short half-lives, and hence need to be given multiple times daily, are good candidates for modified drug delivery systems. However, desmopressin exhibits low bioavailability, which may be due to saturation of receptor sites. Also experimentally, desmopressin, a polypeptide, was found to be stable only in a narrow pH range of about 4-5, more stable at around 4-4.5. Hence in the gastrointestinal tract it is quickly degraded, more in certain environments where factors such as enzymes, adverse pH, P-gp inhibitors, etc. are present. Considering these factors, a prolonged release of desmopressin from a dosage form as it moves through the gastrointestinal tract does not produce satisfactory results. Consequently no satisfactory modified release oral formulations of desmopressin have been reported in the literature.

An enteric coated composition has been described in United States Patent No 5,763,405, which claims an oral pharmaceutical composition comprising desmopressin, an enteric coat soluble at and above pH 5.5, selected from polymers having dissociable carboxyl groups, and a buffering agent buffering at a pH of from 2 to 6. It relates to compositions of desmopressin, which comprise of active ingredient and buffer formed into particles, and the particles contained in the tablets or capsules are enteric coated for delayed release of its contents in the upper part of the small intestine. The buffers are acidic buffers which prevent or delay an increase in the pH as the contents of the stomach pass into the intestine. The patent does not address the issues of dose, duration of action, frequency of administration or reduction of side-effects.

There are many references in the prior art describing formulations that provide a modified release of the drug. United States Patent No. 5,413,777 to Sheth et al. relates to a pulsatile once-a-day delivery system for the administration of minocycline, the antibacterial, for the prolonged controlled release of the drug over a period of 24 hrs. United States Patent No. 6,555,136 relates to pulsatile delivery of methyl phenidate and an additional drug using a swelling agent, an osmotic agent and a film-forming polymer. United States Patent No. 6,228,398 relates to modified release compositions which are essentially multiparticulate in nature. The patent chiefly discloses compositions for methylphenidate which are purported to mimic the profile of multiple immediate release doses in vivo by exhibiting well defined peaks and troughs in the plasma profile. None of these patents provide a solution for the specific problems in desmopressin therapy.

Attempts have continued for providing new and improved therapies of desmopressin. The present invention was made as a result of such attempts. To the best of our knowledge, the oral dosage form for desmopressin and/or its pharmaceutically acceptable salts as described in our invention are previously unknown and completely unsuggested by the art.

Accordingly, it is a primary object of the present invention to address the shortcomings in desmopressin therapy by providing a novel and improved oral dosage form of desmopressin.

It is an object to provide an oral dosage form of desmopressin with better stability and efficacy.

It is also an object to provide an oral dosage form of desmopressin with longer duration of action and hence a lesser frequency of administration.

It is a further object of the present invention to provide an oral dosage form of desmopressin with reduced side-effects.

BRIEF DESCRIPTION OF THE INVENTION

The above objects are realized by the oral dosage form of the invention, which exhibits modified release of desmopressin. The dosage form is adapted to release, upon oral administration, two or more amounts of desmopressin in a pulsatile manner.

The dosage form comprises of two or more individual dosage units, each containing a suitable amount of desmopressin. Typically, there is present an immediate release dosage unit which releases an amount of desmopressin substantially immediately upon administration and one or more delayed release dosage units which release their amounts after predetermined time intervals. The delayed release dosage units comprise of desmopressin and a coating or a matrix of a suitable delayed release material.

The dosage form of the invention contains a therapeutically effective amount of desmopressin, typically in the range of about 20µg to about 300µg per tablet. This total effective unit dose is distributed within various dosage units, such that each dosage unit comprises of a particular amount of desmopressin. These amounts and release profile of desmopressin from the dosage form is adapted such that the dosage form is effective for prolonged duration of action, preferably over about 24 hours, suitable for once daily dosing. Also, there may be and improved absorption of desmopressin, thus higher bioavailability and reduced dose, resulting in reduced incidence and intensity of side effects, especially those related to water retention.

In a preferred embodiment, there is present an immediate release dosage unit in the multiparticulate form, comprising of powder blend or granules of desmopressin, and a delayed release dosage unit in the form of a coated tablet.

The present invention also provides for a method for preparation of the dosage form of the invention, which comprises the steps of formulating the first amount of desmopressin with suitable additives such as diluents, binders, buffers, lubricants etc to form an immediate release dosage unit, formulating a second amount of desmopressin with a delayed release material to form a delayed release dosage unit, optionally formulating a third amount of desmopressin with a delayed release material to form a second delayed release dosage unit and incorporating all the dosage units together to form the dosage form of the invention.

The present invention further provides for a method of treatment and prophylaxis of diseases such as diabetes insipidus, nocturnal enuresis, nocturia and urinary incontinence in a mammal comprising administering to the mammal in need of such treatment the dosage form of the invention.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows the dissolution profile of an illustrative dosage form of desmopressin "Test" from Example 1. The values are given in Table 3. The profile of test sample clearly demonstrates release of a first rapid 'pulse', followed by a lag phase and then an extended release 'pulse' of desmopressin.

Figure 2 shows the dissolution profile of an illustrative dosage form of desmopressin "Test" from Example 2. The values are given in Table 5. The profile of test sample clearly demonstrates release of 2 distinct 'pulses'.

Figure 3 shows the comparative pharmacodynamic parameters, represented as mean Urine Osmolality and Urine Volume values for both Test "T" and Reference "R" (Minirin® tablet 0.1mg). The data has been represented as a bar graph.

DETAILED DESCRIPTION OF THE INVENTION

As disclosed herein and as used in the compositions and methods of the present invention, the term 'desmopressin', includes desmopressin, any of its pharmaceutically acceptable salts, such

as desmopressin acetate, and any of its conjugates, derivatives, prodrugs and natural and synthetic analogs.

For the purpose of the present invention, the term 'substantially no release' is defined as release of the drug from the dosage form which ranges from about 0% to about 20% of the total dose.

The dosage unit, from which the drug release commences substantially immediately, i.e. within an hour of administration, with or without an initial time delay, is the 'immediate release dosage unit' and the dosage unit from which the drug release commences after a specified period of substantially no drug release, is the 'delayed release dosage unit'. Initial time delay as used herein is the duration of time between administration of the dosage form and the release of desmopressin from it.

The term 'dosage unit' in the present context refers both to single unit e.g. a tablet or a mini-tablet or any other form known in the art and multiple units, which represents a plurality of individual units, and in accordance with the present context multiple units refers to granules, beads, pellets, powder or any other form known in the art. The 'dosage form' contains the dosage units and includes capsule, tablet, sachet, liquids or any other relevant dosage form known within the art. Preferred dosage form is solid oral dosage form of desmopressin and/or its pharmaceutically acceptable salts.

In accordance with the present invention, desmopressin is provided in a modified release oral dosage form. Modified release encompasses any release which is not a release as obtained from a conventional immediate release dosage form. The dosage form exhibits a pulsatile release, described in more details below.

Pulsatile release indicates a plurality of drug amounts released at spaced time intervals. Generally, upon ingestion of the dosage form, release of the first amount is substantially immediate, with or without an initial time delay, followed by release of additional 'pulses' of amounts, each after a predetermined time interval.

The first amount of the total therapeutically effective dose of desmopressin from the oral dosage form of the invention is provided as an initial release pulse, which is followed by one or more delayed release pulses such that a second and optionally third or more delayed amount of desmopressin is released from the dosage form. Between two subsequent pulses is a lag time period, during which substantially no drug is released.

The dosage form comprises of an immediate release dosage unit, a delayed release dosage unit and optionally second or more delayed release dosage units. The immediate release dosage unit comprises a first amount of desmopressin that is released substantially immediately following oral administration of the dosage form, with or without an initial time delay. The delayed release dosage unit comprises a second amount of desmopressin and a means for delaying release of the second amount until about 2 hours to about 12 hours following oral administration of the dosage form. The second delayed release dosage unit, when present, comprises a third amount of desmopressin and a means for delaying release of the third amount until at least 3 hours to about 24 hours following oral administration of the dosage form. Further delayed release dosage units, if present, comprise of further amounts which are more subsequently delayed.

As encompassed by the invention, the release of an amount of desmopressin from each dosage unit may be rapid (i.e. 'rapid release' up to 2 hours) or the release may be extended over a period of time (i.e. 'extended release' over more than about 2 hours to about 18 hours) Thus the dosage form may be manufactured in a combination of rapid release and/or extended release amounts. For example, it may be a combination of two rapid release dosage units, or a combination of three rapid release dosage units, or a combination of first rapid release and second extended release dosage units, or a combination of first extended release and second rapid release dosage units, or a combination of two or more extended release dosage units and so on. On administration, the dosage form releases desmopressin amounts as per the desired pulsatile profile. On absorption, this may lead to any type of pulsatile or continuous profile in vivo, depending upon the formulation.

The dosage form of the invention contains a therapeutically effective amount of desmopressin effective over a prolonged period of time, preferably over a period of about 24 hours, given as once daily dosing. The amount is typically in the range of about 20μg to about 300μg per tablet, preferably from about 20μg to about 200 μg per tablet. This total effective unit dose is

distributed within various dosage units, such that each dosage unit comprises of a particular amount of desmopressin. Approximately 10 to 90 % w/w, preferably 30 to 70 % w/w, of desmopressin is present in the immediate release dosage unit, and 90 to 10 % w/w, preferably 70 to 30 %, of the total amount of desmopressin is present in the subsequent delayed release dosage unit/s.

The various embodiments of the invention are described as follows:

An embodiment of the invention is a capsule which contains dosage units comprising of desmopressin-containing particles (i.e. beads, pellets, powder blend, granules, etc.), each dosage unit exhibiting a different release profile. The desmopressin containing particles are prepared by processes commonly known in the art. For example, the powder blend is manufactured by mixing an effective quantity of desmopressin with suitable additives. Granules can be prepared by processes such as wet granulation, dry granulation, slugging or as coated cores. Pellets are prepared by extrusion spheronization. The dosage units may also be prepared from beads which consist of inert supports, such as sugar or starch spheres, on which desmopressin and optionally additives are loaded, or by creating core tablets comprising the drug and additives.

The desmopressin-containing particles of the immediate release dosage unit are generally uncoated; however they may also be coated, depending on the release profile desired. For a rapid release profile, the particles may be coated with conventional polymers such as low viscosity celluloses and cellulose derivatives, vinyl polymers and derivatives, carbohydrates and derivatives, acrylates, methacrylates and the like, in low percentages. For extended release, the release rate may be controlled by coating with rate controlling polymers or by dispersing the drug in a rate controlling polymeric matrix. Such rate controlling polymers may include cellulose derivatives, acrylates, methacrylic acid derivatives, vinyl polymers, polysaccharides, gums, waxes, lipids and combinations thereof.

The release of desmopressin from delayed release dosage units can be delayed by coating the units with polymers such as pH dependent polymers, pH independent polymers, water insoluble polymers and the like. The polymers and their concentrations can be chosen depending upon the release profile desired. Alternatively, desmopressin may be dispersed in a polymeric matrix which controls its release from the dosage unit. Each delayed pulse is formulated, by the proper

choice of additives and their concentrations, to release the drug at the predetermined time and rate.

The desmopressin containing particles of each dosage unit are then filled into the capsule where each dosage unit delivers its amount at the predetermined time and rate. Alternatively, one or more dosage units are present in the form of tablets or minitablets. In such a case, desmopressin is formulated with suitable additives and compressed to form a tablet or minitablet. The tablets may be uncoated or coated with functional polymers as per the release profile desired. Thus the capsule may contain the dosage units either in multiparticulate form or one or more dosage units are in the form of tablets or minitablets.

The dosage form according to this invention may be in the form of liquid oral dosage form comprising a part of dose of desmopressin in dissolved state and remaining part of the dose dispersed in a suitable vehicle along with additives commonly used as part of suspension compositions known in the art. The liquid may alternatively be filled in soft gelatin capsules for oral administration.

An alternate embodiment of the invention is a tablet dosage form. All dosage units in this case, are compacted into a single tablet where they are present as a simple admixture with various additives which aid in the compaction process. Or each dosage unit may be compressed into a discrete layer to form a multilayered tablet, wherein each layer exhibits a different desmopressin release profile. Alternatively, the tablet may be compression coated, wherein the outer layer releases desmopressin substantially immediately on oral administration and the inner layer/layers release the drug after a predetermined lag time at the desired release rate. The term 'lag time' as used herein refers to the period of substantially no release.

Another embodiment is a coated core composition, which comprises an inner desmopressin containing core, surrounded by at least one desmopressin containing layer. The outermost layer contains the immediate release amount of desmopressin. This layer may optionally have an overlying layer of polymeric coating of rate controlling polymers for a desired release rate; or of non rate controlling polymers for aesthetics and better handling capability. The inner core is formulated as compressed delayed release beads or granules, or manufactured as a conventional

core, coated with a bioerodible polymeric layer which controls the release rate and time. If the dosage form provides additional pulses, then additional layers are interposed between the inner core and outer layer, which release desmopressin at the predetermined time.

In a preferred form, satisfactory results are obtained with solid dosage forms, such as a hard gelatin capsule which contains an immediate release dosage unit and one delayed release dosage unit, described as follows. The dosage form releases not more than 70% of desmopressin within 1 hour and not less than 85% of desmopressin within 20 hours of oral administration.

The dosage units comprise of desmopressin formulated with various additives which aid in the manufacture of the dosage form. The additives used are those commonly known in the art, such as diluents, fillers, binders, disintegrants, polymers, lubricants, glidants, surfactants, stabilizers, extrusion aids, penetration enhancers, coating aids, buffers, colorants, etc. An extensive list of the additives that may be considered in practicing the present invention can be found in the "Handbook of Pharmaceutical Excipients" Ed. A.H. Kibbe, 3rd edition, American Pharmaceutical Association, USA and Pharmaceutical Press, UK, 2000.

The immediate release dosage unit in this preferred form is generally manufactured in the form of granules, or as a simple blend of desmopressin with diluents such as lactose, and microcrystalline cellulose. Binders, such as starch derivatives, may be included for better cohesiveness. Dry binders can simply be blended with the rest of the ingredients. Binders can also be used in combination with fluids, such as water, alcohols, or hydro alcoholic mixtures to form granules by the wet granulation method. In the final step, lubricants are added, for better flow. Commonly used lubricants are magnesium stearate, stearic acid etc.

Desmopressin, a polypeptide, is highly susceptible to degradation in the gastro-intestinal tract, via proteolysis, by various enzymes, and the degradation is accelerated in the extreme pH ranges. Experimentally, highest stability of the drug has been found to be at a pH range of about 4-6. Buffers are included in the dosage form, which, upon release in the gastro-intestinal tract, provide desmopressin with a microenvironment in the 3 – 6 pH range, more specifically in the range of pH 4-6, and thus protect it from degradation. For dosage units released in the stomach or in the acidic environments, buffers used in the invention include, but are not limited to,

sodium bicarbonate, effersoda (combination of sodium carbonate and sodium bicarbonate), sodium borate, sodium carbonate, triethanolamine, sodium citrate dihydrate, trisodium citrate, meglumine, L-lysine, L-histidine, protamine. The buffering agent is included in a range of about 2.0% w/w to about 90% w/w of the dosage form weight, preferably about 10% w/w to about 80% w/w of the dosage form weight and more preferably about 20% w/w to about 60% w/w of the dosage form weight. Preferred buffering agent is sodium bicarbonate or effersoda. The buffering agent may be included in the dosage unit either by mixing with the drug and other ingredients homogenously, or may be layered on the granules, pellets or beads to form a coating. The desmopressin dosage form comprising the said dosage unit when added to water gives a pH of about 9.0 and is stabilized in the acidic pH to a pH range of 4 – 6. This prevents degradation of the composition in the stomach, and may thereby achieve higher absorption of desmopressin.

The delayed release unit in the preferred form is manufactured in the form of granules, which are compressed into a tablet. Granules of desmopressin are prepared by mixing the drug with a suitable diluent, like lactose or microcrystalline cellulose. Binder is added for cohesiveness. A disintegrant, like pregelatinized starch, sodium starch glycolate, low substituted hydroxypropyl cellulose, crosslinked povidone, ac-di-sol etc. is added to ensure disintegration of the dosage unit on imbibing fluids and the release of desmopressin therein. Hydrating materials like polymers which swell on imbibing fluids from the gastrointestinal tract like hydroxypropyl methyl cellulose, hydroxypropyl cellulose and gums like xanthan gum, guar gum, locust bean gum and other water-swellable materials are added. These help in creating a 'burst effect' of the dosage unit at a predetermined time, based on the amount and ratio of such materials used in the dosage form. Preferably the hydroxypropyl cellulose is low-substituted hydroxypropyl cellulose available in various grades, most preferred is L-HPC; LH-11. The ratio of xanthan gum and L-HPC used is in the range of 1:0.5 to 1:5. Xanthan gum and hydroxypropyl cellulose are each included in the range of about 0.5 % to about 20%, preferably about 1.0% to about 10% of the dosage form weight. All the ingredients are mixed adequately and the blend is lubricated with magnesium stearate for better flow during the manufacturing process. The lubricated blend or granules thus prepared are subject to compression in a suitable tablet press, such as a rotary compression machine. Tablets containing the desired dose of desmopressin are compressed at a hardness value sufficient to withstand further processing and handling and at the same time, capable of disintegrating and releasing the drug.

The epithelial cells lining the luminal side of the GIT are a major barrier to drug delivery following oral administration. Most orally administered drugs are absorbed by passive transport. Drugs, which are lipophilic, permeate the epithelium by the transcellular route whereas drugs that are hydrophilic are restricted to the paracellular route. Paracellular pathways occupy less than 0.1% of the total surface area of the intestinal epithelium. Further, tight junctions, which form a continuous belt around the apical part of the cells, restrict permeation between the cells by creating a seal between adjacent cells. Thus, oral absorption of hydrophilic drugs such as peptides can be severely restricted. Other barriers to absorption of drugs may include hydrolyzing enzymes in the lumen brush border or in the intestinal epithelial cells, the existence of the aqueous boundary layer on the surface of the epithelial membrane which may provide an additional diffusion barrier, the mucus layer associated with the aqueous boundary layer and the acid microclimate which creates a proton gradient across the apical membrane. Absorption, and ultimately bioavailability, of a peptide drug is thus, highly reduced.

One of the strategies for delivering drugs across the GIT cell layers is the use of permeation enhancers. They increase the absorption of peptides by numerous mechanisms, like, dissolving the barrier mucus layer, reversible interaction with GI epithelial cells, transient opening of paracellular junctions etc. Numerous permeation enhancers are known in the literature. Examples of a few which can be used in our invention include 23-lauryl ether, Aprotinin, Azone, Benzalkonium chloride, Cetylpyridinium chloride, Cetyltrimethylammonium bromide, Dextran sulfate, Lauric acid, Lysophosphatidylcholine, Menthol, Methoxysalicylate, Methyloleate, Oleic acid, Phosphatidylcholine, Polysorbate 80, Sodium EDTA, Sodium glycocholate, Sodium glycodeoxycholate, Sodium lauryl sulfate, Sodium salicylate, Sodium taurocholate, and Sodium taurodeoxycholate. Alternatively, certain other known bioavailability enhancers like P-Glycoprotein inhibitors (P-gp inhibitors) may also be included to improve the bioavailability of drug in the dosage form of the present invention.

Accordingly, about 0.05 % w/w to about 90.0% w/w of the dosage form of permeation enhancers are added, particularly in the delayed release dosage units.

The delay in drug release from the units may be caused by mixing the drug with rate controlling materials as a matrix but in the preferred form it is caused by coating the units with a rate controlling material, typically although not necessarily, a polymeric material. Particularly

preferred coating materials are bioerodible, water insoluble, gradually hydrolysable, gradually water soluble polymers, pH dependent and independent polymers and/or enzymatically degradable polymers. The time and rate of drug release can be controlled by a combination of the choice of polymers and the average quantity deposited on the dosage units.

Suitable membrane coating materials or polymers in matrix for effecting delayed release include, but are not limited to: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, cellulose ester-ether phthalate, hydroxypropylcellulose phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, hydroxypropylmethyl cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, with a terpolymer of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride, polymers having dissociable carboxyl groups, other particularly preferred polymers like; vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; alkylene oxide homopolymers such as polypropylene oxide, and ethylene oxide homopolymers; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate.

Alternatively, the matrix or the polymeric coating layer may be comprised of other substances that are capable of becoming freely permeable following hydration in aqueous fluids. Such substances include polysaccharides, such as gelatin, saccharose, sorbitol, mannose, and haluronic acid; polyaminoacids; polyalcohols; polyglycols; and the like.

Preferred films are made from Cellulose Acetate polymers or Ethyl cellulose polymers. Cellulose acetate is commercially available in various grades. These are non-enteric cellulose esters, which do not show pH-dependant solubility characteristics. Their films are essentially insoluble yet semi permeable. Controlled release through the films can be achieved by incorporation of water-soluble materials in the films to increase the ability of the drug to diffuse

through it. The cellulose acetate polymer may be present in an amount ranging from about 1.0% to about 80% of the formulation, preferably about 5% to about 60% and more preferably from about 10% to about 50%.

Ethyl Cellulose is an insoluble polymer which does not readily dissolve or disperse in the stomach or intestines. It is used in conjunction with water soluble materials which eventually dissolve upon administration and create pores in the ethyl cellulose coat through which the drug is released. Suitable water soluble components are polymers like hydroxypropyl methyl cellulose and hydroxypropyl cellulose.

Preferably, the coating comprises of ethyl cellulose and hydroxypropyl cellulose in a ratio of about 1:0.1 to about 1:1. The percentage of coating varies as per the release profile desired, although, in general, satisfactory results are obtained by a tablet weight gain of about 2% w/w to 50% w/w.

The polymer compositions are normally plasticized, to increase the flexibility of the film. Typical plasticizers used are polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, acetyl tributyl citrate, castor oil and acetylated monoglycerides; although any other suitable plasticizer may also be used. Preferably, a plasticizer, such as triethyl citrate or acetyl tributyl citrate, may be used in a concentration of about 5% to about 50% of the dry weight of the polymers.

The coating composition may also include other conventional additives, such as pigments, colorants, stabilizing agents, glidants, etc.

Solvents used for dissolving and coating the polymeric films on the dosage units can be conveniently either aqueous or organic. Aqueous dispersions of Ethyl cellulose are also readily available, such as Aquacoat® by FMC Biopolymer. Examples of organic solvents which can be utilized are alcohols such as ethanol, ketones such as acetone, and halogenated hydrocarbons such as dichloromethane.

Conveniently, mixtures of organic based solvents, such as isopropyl alcohol/acetone, are used in various ratios as required.

The coating solution, comprised of the above described ingredients is coated on the dosage units by spraying it, utilizing processes such as conventional pan coating, airless spray technique, fluidized bed coating and the like. Detailed information concerning materials, equipment and processes for preparing tablets and delayed release dosage, reference may be made to Pharmaceutical Dosage Forms: Tablets, eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989).

It may also be desirable to prime the surface of the dosage units before the functional coating, or lay a seal coat over the functional layer. In such cases, a thin hydroxypropyl methylcellulose (HPMC) film may be utilized. While HPMC is typically used, other polymers such as hydroxypropyl cellulose (HPC) can also be used.

The blend or granules of the immediate release dosage unit thus prepared, corresponding to the desired amount of desmopressin, and coated tablet of the delayed release dosage unit is filled into a capsule to form the dosage form of the invention.

Thus, in an exemplary form, the present invention provides a capsule dosage form of desmopressin comprising an immediate release dosage unit in the form of desmopressin containing particles. The particles together contain the first amount of desmopressin which is released substantially immediately upon administration. In addition, the dosage form contains a delayed release dosage unit in the form of a coated tablet. The tablet contains the remaining amount of desmopressin, which is released after a delay of about 2 to 12 hours. When evaluated for in-vitro dissolution in water, using USP dissolution Type II apparatus, the dosage form generally releases not more than 70% of total desmopressin within 30 minutes, about 0 to 20% of total desmopressin between 30 minutes and 2 hours and not less than 85% of total desmopressin within 12 hours. Preferably, the dosage form exhibits a release of about 5 to 50% of total desmopressin in 30 minutes, about 0 to 20% of total desmopressin between 30 minutes to 3 hours and about 30 to 95% of total desmopressin between 2 to 10 hours.

If the dosage form is designed to contain an additional dosage unit, this unit may release the additional amount of desmopressin about 3 hrs to about 24 hrs after oral administration. In such cases, release may take place in the lower part of the gastrointestinal tract and colon. For such purpose, polymers and other materials are used that enable drug release in the colon. These may include the aforementioned materials, or other materials, such as polysaccharides, mucopolysaccharides like pectin, chitosan; and hydrocolloid gums like karaya gum, guar gum, gum tragacanth etc.

The dosage form of the invention is particularly useful for the prophylaxis and/or treatment of disorders such as diabetes insipidus, nocturnal enuresis, nocturia and urinary incontinence.

In diabetes insipidus, generally about 0.1 to 0.2 mg conventional desmopressin tablets are administered 2 to 3 times daily. This need for multiple daily dosing over a prolonged period causes inconvenience to patients and is a major disadvantage. Also, continued water retention caused by dose accumulation, leads to side effects such as bloating, fluid retention and headache. The dosage form of the present invention is effective over a prolonged period of time, especially over about 24 hours. It also provides for a period of lag time, where the drug concentration is low. This minimizes dose accumulation and reduces the occurrence of side effects mainly, those caused due to water retention.

For nocturnal enuresis, preferably, a single effective dose of desmopressin is administered to a person at bed time. However in some instances, a second dose has to be administered during the daytime for continued effect. This second dose may lead to side effects, like bloating, fluid retention and headache. Also in some instances early morning bed wetting is not prevented by the conventional dosage form. The dosage form described in the present invention has higher plasma levels at night, when effectiveness is required and exhibits lower but effective plasma levels throughout the day, when fluid intake is higher. Thus, early morning bed wetting would also be prevented.

The dosage form of the invention can thus be tailor-made for specific purposes. For example, the dosage form can have a higher first amount and subsequently lower amount/s particularly to treat nocturnal enuresis; or it can have a lesser first amount and higher subsequent amount/s particularly to treat diabetes insipidus.

Comparative pharmacodynamics and in vivo evaluation:

The antidiuretic effect and pharmacokinetics were investigated in a randomized, single-dose, cross-over study, conducted in six healthy hydrated human volunteers after oral administration of 0.1 mg desmopressin. The antidiuretic activity was measured by determination of urine osmolality and urine volume (diuresis) every 2 hours over a period of 24 hours for both test product "T" (pulsed release desmopressin acetate capsules prepared according to the present invention) and reference product "R" (marketed Minirin® tablets, 0.1 mg).

Results are shown in following Table 1 and the same illustrated in Figure 3.

Table 1:

Mean peak pharmacodynamic parameters (SD) in healthy male volunteers:

Treatment	Urine Volume in mL/min	Maximum Urine Osmolality in mOsm/kg
Test product	0.40 (0.06)	770.8 (135.26)
Reference product	0.48 (0.11)	706.2 (61.92)

As the urine osmolality increased, the urine volume was decreased; this indicated an inverse co-relation for urine osmolality and volume in the obtained results. The mean peak values for both osmolality and volume was determined, increased osmolality and reduced urine volume in test product indicates decreased diuresis. Urine osmolalities analyzed as area under the time curve, was raised after treatment with the test product (For T, mean AUC 9996.09, std error mean 826.4; For T, mean AUC 8968.63, std error mean 561.7), which can be co-related to reduced values for Urine volume (For T, mean AUC 178.01, std error mean 15.0; For T, mean AUC 192.38, std error mean 15.1).

Thus, the modified release solid oral dosage form of desmopressin of the present invention provides therapeutic efficacy over a period of about 24 hours, as is seen from the above data. Due to the buffered pH microenvironment, there is less degradation of desmopressin. Also, the release profile prevents accumulation and possible saturation of the absorption mechanisms. These characteristics provide for a better availability of the drug at the absorption site and lead to improved absorption. Reduced accumulation will also cause less incidence and intensity of

one or more side effects, especially those related to water accumulation, such as headache, nausea/vomiting and bloating.

Thus, the present invention provides for a superior overall management of antidiuretic therapy.

As used in this specification and the appended claims, it is to be understood that the singular forms such as "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

Various modifications of the methods of the invention may be made without departing from the spirit or scope of the invention. The following non-limiting examples illustrate an embodiment of the invention and should not be construed to limit the scope of the invention.

EXAMPLES

Example 1

A dosage form was manufactured containing two dosage units as per the invention. The first immediate release dosage unit was manufactured by blending the ingredients given in the Table 2. The delayed release dosage unit was manufactured by blending the given ingredients and compressing them into a tablet using a suitable tablet compression machine. The tablets were then coated to a weight gain of 8-12% by spraying them with the coating polymer solution, using equipments such as pan-coaters or fluid bed coaters. Blend of the immediate release unit corresponding to the desired amount and one tablet of the delayed release unit were filled into a hard gelatin capsule.

Table 2:

Immediate release dosage unit

Ingredients	**Quantity in mg.**
Desmopressin acetate	0.03
Lactose monohydrate	195.7
Sodium bicarbonate	375.0
Magnesium stearate	4.31

Delayed release dosage unit

Ingredients	Quantity in mg.
Desmopressin acetate	0.07
Lactose monohydrate	72.04
Croscarmellose sodium	15.0
Xanthan gum	22.0
Hydroxypropyl cellulose	8.4
Magnesium stearate	1.5
Coating composition	
Ethyl cellulose 7 cps	7.5
Hydroxypropyl cellulose	0.58
Acetyl tributyl citrate	1.9

The dosage form was tested for in vitro dissolution properties using USP dissolution apparatus II in water. The dissolution was carried out for 10 hrs and samples analyzed by HPLC.

Table 3:

Time (hrs)	Mean % drug release
0.5	31.5
1	33.6
2	32.8
4	33.6
6	45.0
8	65.2
10	80.0
12	92.0

Example 2

Manufacturing procedure followed was same as Example 1.

Table 4:

Immediate release dosage unit

Ingredients	**Quantity in mg.**
Desmopressin acetate	0.03
Lactose monohydrate	195.0
Sodium bicarbonate	375.0
Magnesium stearate	4.3

Delayed release dosage unit

Ingredients	**Quantity in mg.**
Desmopressin acetate	0.07
Lactose monohydrate	36.7
Xanthan gum	30.0
Hydroxypropyl cellulose	42.0
Magnesium stearate	1.5
Coating composition	Quantity in gm per 1000gm of solution
Ethyl cellulose 7 cps	30.0
Hydroxypropyl methyl cellulose	1.8
Acetyl tributyl citrate	6.0

The dosage form was tested for in vitro dissolution properties using USP dissolution apparatus II in water. The dissolution was carried out for 10 hrs and samples analyzed by HPLC.

Table 5:

Time (hrs)	**Mean % drug release**
0.5	34.4
1	42.8
2	41.7
4	44.2
6	100.7
8	107.6
10	106.5

Example 3

Manufacturing procedure followed was same as Example 1.

Table 6:

Immediate release unit

Ingredient	**Quantity in mg.**
Desmopressin acetate	0.02
Lactose	42.98
Meglumine	50.0
Hydroxypropyl methyl cellulose (HPMC E15)	5.0
Magnesium stearate	1.5
Polyethylene glycol 400	0.5
Purified water	Qs.

Delayed release unit

Ingredient	**Quantity in mg.**
Desmopressin acetate	0.02
Lactose monohydrate	42.98
Lecithin	0.3
Magnesium stearate	1.0
Coating composition	
Cellulose Acetate CA 320S	53.25
Cellulose Acetate CA 398 10	8.01
Hydroxypropyl methyl cellulose (HPMC E15)	5.72
Polyethylene glycol PEG 8000	7.25

Example 4:

Manufacturing procedure followed is same as Example 1.

Table 7:

Immediate release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.02
Lactose	90.98
Sodium carbonate	200.0
Hydroxypropyl methyl cellulose (HPMC E15)	5.0
Magnesium stearate	4.0
Polyethylene glycol 400	0.5
Purified water	Qs.

Delayed release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.03
Lactose monohydrate	97.67
Vitamin E-TPGS	0.3
Magnesium stearate	2.0
Coating composition	
Cellulose Acetate CA 398 10	48.26
Hydroxypropyl methyl cellulose (HPMC E15)	5.72
Polyethylene glycol PEG 3350	7.25

Example 5:

Desmopressin was coated on lactose and divided equally into two parts.

Part of the above active material was coated with coat Eudragit E100 and dried at 40° to 45°C. The dried powder was blended with sodium bicarbonate and magnesium stearate.

Second part of the active material was granulated with lactose and Gelucire 44/14, and mixed with magnesium stearate. This blend was compressed into tablets and coated with a solution of cellulose acetate, hydroxypropyl methyl cellulose and polyethylene glycol to a suitable weight gain. Blend of the immediate release unit corresponding to the desired amount and one tablet of the delayed release unit were filled into a hard gelatin capsule.

Table 8:

Immediate release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.05
Lactose	89.95
Sodium bicarbonate	500.0
Eudragit E100	5.0
Magnesium stearate	5.0

Delayed release unit

Ingredient	Quantity in mg.
Second part of Desmopressin acetate coated on lactose	Equivalent to 0.025mg Desmopressin acetate
Lactose monohydrate	99.525
Gelucire 44/14	0.3
Purified water	qs
Magnesium stearate	1.0
Coating composition	
Cellulose Acetate CA 320S	53.25
Hydroxypropyl methyl cellulose (HPMC E15)	5.72
Polyethylene glycol PEG 3350	7.25

Example 6:

In this embodiment, wet granulation was carried out in the manufacturing of granules for immediate release and delayed release units. Immediate release granules were formulated as a blend ready for filling and delayed release granules were compressed to form tablets and coated with the Cellulose Acetate coating solution.

The final dosage form was obtained by filling the immediate release granules along with delayed release tablet into empty hard gelatin capsule shell using a suitable capsule filling equipment.

Table 9:

Immediate release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.03
Lactose monohydrate	92.97
L-lysine	100.0
Polyvinyl pyrrolidone PVP K-30	6.0
Purified water	qs
Magnesium stearate	1.0

Delayed release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.02
Lactose monohydrate	92.68
Poloxamer F-68	0.3
Polyvinyl pyrrolidone PVP K-30	6.0
Magnesium stearate	1.0
Coating composition	
Cellulose Acetate CA 320S	53.25
Cellulose Acetate CA 398 10	8.01
Hydroxypropyl methyl cellulose; (HPMC E15)	5.72
Polyethylene glycol PEG 8000	7.25

Example 7:

The procedure followed was the same as example 6, except the dosage form was formulated as a compression coated tablet. The delayed release coated tablet was placed in the compression die and immediate release blend was filled around it to for the compression coated formulation.

Table 10:

Immediate release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.06
Lactose monohydrate	93.83

Sodium glycine carbonate	250.0
Polyvinyl pyrrolidone PVP K-30	6.0
Purified water	qs
Magnesium stearate	1.0

Delayed release unit

Ingredient	**Quantity in mg.**
Desmopressin acetate	0.02
Lactose monohydrate	93.50
Polaxamer F-68	0.3
PVP K-30	6.0
Magnesium stearate	1.0
Coating composition	
Eudragit RL/RS	50.0
Hydroxypropyl methyl cellulose; (HPMC E15)	5.72
Polyethylene glycol PEG 6000	7.25

Example 8:

The procedure followed was the same as example 1.

Table 11:

Immediate release unit

Ingredient	**Quantity in mg.**
Desmopressin acetate	0.02
Dibasic calcium phosphate	94.83
Meglumine	100.0
Hydroxypropyl methyl cellulose (HPMC E5LVP)	5.0
Magnesium stearate	1.0
Polyethylene glycol 400	0.5
Purified water	Qs.

Delayed release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.02
Dibasic calcium phosphate	99.53
Polysorbate 80	0.3
Magnesium stearate	0.15
	100 mg
Coating composition	
Ethyl Cellulose 10cps	40.0
Hydroxypropyl methyl cellulose (HPMC E15)	5.72
Polyethylene glycol PEG 8000	7.25

Example 9:

The procedure followed was the same as example 6.

Table 12:

Immediate release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.02
Dibasic calcium phosphate	93.83
Disodium citrate	200.0
Polyvinyl pyrrolidone PVP K-30	6.0
Purified water	qs
Magnesium stearate	2.5

Delayed release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.02
Dibasic calcium phosphate	93.53
Vitamin ETPGS	0.3
PVP K-30	6.0
Magnesium stearate	0.15
Coating composition	

Cellulose Acetate CA 320S	53.25
Cellulose Acetate CA 398 10	8.01
Hydroxypropyl methyl cellulose; (HPMC E15)	5.72
Polyethylene glycol PEG 8000	7.25

Example 10:

The procedure followed was the same as example 6.

Table 13:

Immediate release unit

Ingredient	**Quantity in mg.**
Desmopressin acetate	0.02
Dibasic calcium phosphate	93.83
Disodium citrate	100.0
Polyvinyl pyrrolidone PVP K-30	6.0
Magnesium stearate	0.15
Purified water	qs

Delayed release unit

Ingredient	**Quantity in mg.**
Desmopressin acetate	0.05
Dibasic calcium phosphate	93.50
Polysorbate 80	0.3
PVP K-30	6.0
Magnesium stearate	0.15
Coating composition	
Cellulose Acetate CA 320S	53.25
Cellulose Acetate CA 398 10	8.01
Hydroxypropyl methyl cellulose; (HPMC E15)	5.72
Polyethylene glycol PEG 8000	7.25

Example 11:

Blend of the immediate release unit was prepared. Mixture of desmopressin acetate and lactose was granulated with an aqueous solution of lecithin, dried, blended with magnesium stearate and compressed into tablets of suitable size. The tablets were coated with the coating solution of Cellulose Acetate, Hydroxypropyl methyl cellulose and Polyethylene glycol to a suitable weight gain. The final dosage form was obtained by filling the IR blend along with delayed release tablet into empty hard gelatin capsule shell.

Table 14:

Immediate release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.02
Lactose monohydrate	20.0
Meglumine	50.0
Magnesium stearate	1.0

Delayed release unit

Ingredient	Quantity in mg.
Desmopressin acetate	0.02
Lactose monohydrate	42.98
Lecithin	0.3
Magnesium stearate	1.0
Coating composition	
Cellulose Acetate CA 320S	53.25
Cellulose Acetate CA 398 10	8.01
Hydroxypropyl methyl cellulose (HPMC E15)	5.72
Polyethylene glycol PEG 8000	7.25

Claims:

1. An oral dosage form comprising desmopressin, the dosage form being adapted to exhibit a modified release of desmopressin.

2. The oral dosage form of Claim 1, adapted to release two or more amounts of desmopressin upon oral administration.

3. The oral dosage form of Claim 1, adapted to release two or more amounts of desmopressin upon oral administration, in a pulsatile manner.

4. The oral dosage form of Claim 1, comprising an immediate release dosage unit comprising a first amount of desmopressin and one or more delayed release dosage units comprising subsequent amounts of desmopressin.

5. The oral dosage form of Claim 4 comprising

an immediate release dosage unit comprising a first amount of desmopressin that is released substantially immediately upon oral administration;

a delayed release dosage unit comprising a second amount of desmopressin and a means for delaying release of the second amount of desmopressin until about 2 hours to about 12 hours following oral administration;

and optionally a second delayed release dosage unit comprising a third amount of desmopressin and a means for delaying release of the third amount of desmopressin until about 3 hours to about 24 hours upon oral administration.

6. The oral dosage form of Claim 5, optionally comprising further delayed release dosage units, each unit comprising a further amount of desmopressin and a means for delaying release of the further amount for a specified period upon oral administration.

7. The oral dosage form of Claim 4 comprising 20μg to 300 μg of desmopressin, wherein about 10 to 90% of total desmopressin is present in the immediate release dosage unit and about 90 to 10 % of total desmopressin is present in the delayed release dosage unit/s.

8. The oral dosage form of Claim 4 comprising 20μg to 200 μg of desmopressin, wherein about 30 to 70% of total desmopressin is present in the immediate release dosage unit and about 70 to 30 % of total desmopressin is present in the delayed release dosage unit/s.

9. The oral dosage form of Claim 1 wherein the dosage form is a solid oral dosage form.

10. The oral dosage form of Claim 9 wherein the dosage form is a capsule comprising one or more dosage units which are in the form selected from tablets, minitablets and a plurality of desmopressin containing particles.

11. The oral dosage form of Claim 9 wherein the dosage form is a tablet selected from a single layered tablet, multilayered tablet and compression coated tablet.

12. The oral dosage form of Claim 9 wherein the dosage forms is a coated core composition, comprising an inner desmopressin containing core and at least one overlying desmopressin containing layer.

13. The oral dosage form of Claim 4 comprising an immediate release dosage unit comprising a plurality of desmopressin containing particles, together containing the first amount of desmopressin released substantially immediately upon oral administration; and a delayed release dosage unit in the form of a coated tablet containing the remaining amount of desmopressin released after a delay of about 2 hours to about 12 hours, wherein the oral dosage form is a hard gelatin capsule.

14. The oral dosage form of Claim 4 comprising a buffering agent in the immediate release dosage unit, buffering at a pH of from 3 to 6, wherein the buffering agent is present in the range of about 2% w/w to about 90% w/w of the dosage form weight.

15. The oral dosage form of Claim 14 wherein the buffering agent is selected from the group of sodium bicarbonate, effersoda, sodium borate, sodium carbonate, triethanolamine, sodium citrate dihydrate, disodium citrate meglumine, L-lysine, sodium glycine carbonate, L-histidine and protamine.

16. The oral dosage form of Claim 4 wherein the delayed release dosage unit comprises a delayed release material present in a form selected from a membrane coating and a matrix.

17. The oral dosage form of Claim 16 wherein the delayed release material comprises of a bioerodible polymer selected from the group of cellulose polymers and copolymers, cellulose esters, acrylic acid polymers and copolymers, vinyl polymers and copolymers, alkylene oxide homopolymers, shellac, polysaccharides, mucopolysaccharides, polyaminoacids; polyalcohols; and polyglycols, hydrocolloid gums, waxes and/or derivatives thereof.

18. The oral dosage form of Claim 16 wherein the delayed release material is selected from cellulose acetate and ethyl cellulose.

19. The oral dosage form of Claim 18 wherein ethyl cellulose is used in combination with a cellulose selected from the group of hydroxypropyl cellulose and hydroxypropyl methyl cellulose.

20. The oral dosage form of Claim 19 comprising ethyl cellulose and hydroxypropyl cellulose in a weight ratio of about 1:0.1 to about 1:1 as a membrane coating and when coated on a tablet dosage unit it is coated till a weight gain of about 2% w/w to about 50% w/w of tablet weight.

21. The oral dosage form of Claim 4 comprising a penetration enhancer selected from 23-lauryl ether, Aprotinin, Azone, Benzalkonium chloride, Cetylpyridinium chloride, Cetyltrimethylammonium bromide, Dextran sulfate, Lauric acid, Lysophosphatidylcholine, Menthol, Methoxysalicylate, Methyloleate, Oleic acid, Phosphatidylcholine, Polysorbate 80, Sodium EDTA, Sodium glycocholate, Sodium glycodeoxycholate, Sodium lauryl sulfate, Sodium salicylate, Sodium taurocholate, Sodium taurodeoxycholate, and P-gp inhibitors in the range of 0.05 to 90% w/w of the dosage form.

22. The oral dosage form of Claim 4 wherein the delayed release dosage unit comprises xanthan gum and hydroxypropyl cellulose in a ratio of from 1:0.5 to 1:5

23. The oral dosage form of Claim 1, when tested in a USP Type II apparatus using water, releases not more than 70% of total desmopressin within 30 minutes, about 0 to 20% of total desmopressin between 30 minutes and 2 hours and not less than 85% of total desmopressin within 12 hours.

24. The oral dosage form of Claim 1, when tested in a USP Type II apparatus using water, releases 5 to 50% of total desmopressin in 30 minutes, about 0 to 20% of total desmopressin between 30 minutes to 3 hours and about 30 to 95% of total desmopressin between 2 to 10 hours.

25. A method for preparation of the oral dosage form of Claim1, comprising the steps of formulating a first amount of desmopressin with suitable additives to form an immediate release dosage unit;

formulating a second amount desmopressin with a delayed release material to form a delayed release dosage unit;

optionally formulating a third amount of desmopressin with a delayed release material to form a second delayed release dosage unit;

and incorporating all the dosage units together to form the dosage form of the invention.

26. The method of Claim 25, optionally comprising a step of formulating a further amount of desmopressin with a delayed release material to form a further delayed release dosage unit.

27. The oral dosage form of Claim 1 suitable for once daily administration.

28. A method of treatment and prophylaxis of a disease selected from the group of diabetes insipidus, nocturnal enuresis, nocturia and urinary incontinence in a mammal comprising administering to the mammal in need of such treatment the oral dosage form of Claim 1.

29. An oral dosage form that provides pulsatile release of desmopressin, adapted to produce a therapeutic effect over about 24 hours when administered to a patient in need thereof.

30. The oral dosage form of Claim 29 with reduced incidence and intensity of one or more side effects relative to conventional immediate release desmopressin tablets.

31. The oral dosage form of Claim 1 comprising desmopressin, wherein the dosage form is suitable for once daily administration and releases desmopressin in a pulsatile manner such that not more than 70% of desmopressin is released within 1 hour and not less than 85% of desmopressin is released within 20 hours of oral administration.

32. An oral dosage form that provides pulsatile release of desmopressin to produce a therapeutic effect over about 24 hours when administered to a patient in need thereof, wherein the dosage form provides for improved absorption of desmopressin.

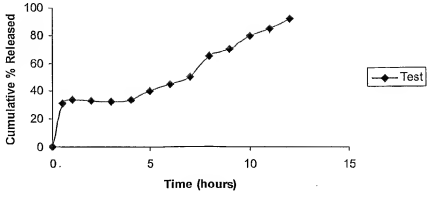

Figure 1

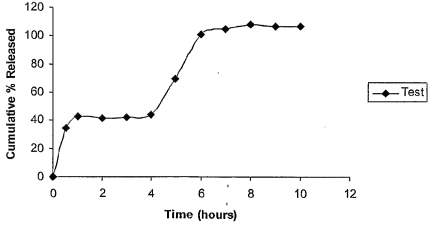

Figure 2

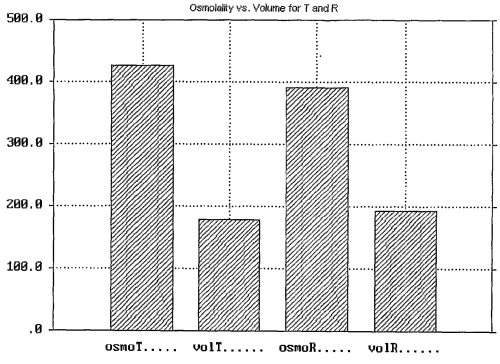
Osmolality vs. Volume for T and R
500.0
400.0
300.0
200.0
100.0
.0
osmoT.....
volT.....
osmoR.....
volR.....

Figure 3

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 July 2007 (26.07.2007)

PCT

(10) International Publication Number
WO 2007/083323 A3

(51) International Patent Classification:
A61K 38/08 (2006.01) *A61K 9/48* (2006.01)
A61K 9/22 (2006.01)

(21) International Application Number:
PCT/IN2007/000022

(22) International Filing Date: 19 January 2007 (19.01.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
101/MUM/2006 23 January 2006 (23.01.2006) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

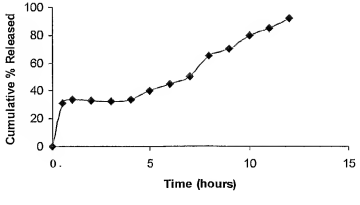
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

(54) Title: MODIFIED RELEASE ORAL DOSAGE FORM COMPRISING DESMOPRESSIN



(57) Abstract: The invention describes a modified release oral dosage form of desmopressin which upon administration releases two or more amounts of desmopressin. The dosage form comprises of individual dosage units, such as an immediate release dosage unit and one or more delayed release dosage units, each comprising of a suitable amount of desmopressin, released after a predetermined time interval. The dosage form of the invention provides a release profile, adapted such that the dosage form exhibits improved efficacy for a prolonged duration of action and provides for an overall superior management of antidiuretic therapy. The invention also provides for method of manufacture of the dosage form of the invention and also method of treatment of diseases such as diabetes insipidas, nocturnal enuresis, nocturia and urinary incontinence in a mammal in need of such treatment.

WO 2007/083323 A3

(88) **Date of publication of the international search report:**
18 October 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2007/000022

A. CLASSIFICATION OF SUBJECT MATTER
IPC[8]: ***A61K 38/08*** (2006.01); ***A61K 9/22*** (2006.01); ***A61K 9/48*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC[8]: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, TXTe, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/091623 A1 (CUMMING et al.) 15 May 2003 (15.05.2003) *paragraphs [0030]-[0051]; claims 1, 9, 11-13, 17-20, 25-37*	1-29, 31, 32
X	WO 2000/013663 A1 (ALZA CORPORATION) 16 March 2000 (16.03.2000) *page 20, lines 8-20; claims 1, 6; figures 1-6*	1, 9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2007 (02.07.2007)	8 August 2007 (08.08.2007)
Name and mailing address of the ISA/ AT **Austrian Patent Office** Dresdner Straße 87, A-1200 Vienna	Authorized officer MOSSER R.
Facsimile No. +43 / 1 / 534 24 / 535	Telephone No. +43 / 1 / 534 24 / 437

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2007/000022

Continuation of first sheet

Continuation No. II:

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 28, 30 because they relate to subject matter not required to be searched by this Authority, namely:

- Although claim 28 concerns a method of treatment of the human or animal body by therapy (see PCT rule 39.1(iv)) the search was carried out and based on the alleged effects.

Claim 30 concerns the number of side effects of a medical treatment. For this subject-matter no search/examination was possible.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 2007/00022

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
US A 2003091623		US	A1	2007148228	2007-06-28
		US	A1	2003091623	2003-05-15
		JP	A	2002537321	2002-11-05
		WO	A1	0050012	2000-08-31
		EP	A1	1154761	2001-11-21
		CA	A1	2363123	2000-08-31
WO A 2000013663		none			